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Fungal keratitis after amniotic membrane placement

Lena Chen *, Deena Dahshan, Thomas Mauger

West Virginia University Department of Ophthalmology, Morgantown, WV, USA

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ABSTRACT

Purpose: We present two cases of fungal keratitis following amniotic membrane transplantation, including *Sistotrema biggsiae* and *Fusarium* keratitis.

Observations: A 76-year-old female with a history of anterior basement membrane dystrophy referred for reduced vision and left eye pain ten days following AMT at an outside facility. Despite topical management, the patient continued to worsen clinically, with a recalcitrant course of Fusarium keratitis requiring conjunctival flap, cryotherapy, and intracameral and intrastromal injection. The second case involved a 46-year-old male with a history of recurrent corneal erosions referred for blurry vision and pain in his left eye seven days following AMT. He was found to have *Sistotrema biggsiae* keratitis and had remarkable visual improvement with topical management.

Conclusions: Fungal keratitis following amniotic membrane placement has not been reported presenting within ten days after transplantation. This is the first report of *Sistotrema biggsiae* infection in humans. This case series highlights the risk of severe recalcitrant microbial keratitis presenting within days after AMT placement and recognizing fungal etiologies not previously reported in literature. The risk of keratitis following AMT should be considered with close patient follow up, especially in patients with monocular vision.

1. Introduction

Amniotic membrane transplantation (AMT) is a widely used management of corneal and conjunctival reconstruction often implemented after failing medical treatment options. Amniotic membranes (AM) are from the innermost layer of fetal membranes, harvested in sterile environments from extensively screened donors undergoing elective cesarean section delivery. AMT has been used as a therapeutic option for corneal ulcers secondary to infection.[1] a.m. can facilitate epithelialization and healing, provide stability for restoring tissue integrity, and act as a patch to promote healing by reducing inflammation and scarring.[1]While AM can be a treatment option for epithelial defects, there are reported cases of microbial infections following AMT.[2]

2. Findings

In this report, we present 2 cases of fungal keratitis following AMT.

2.1. Case 1

The first case involves a 76-year-old female with a history of anterior basement membrane dystrophy (ABMD), referred by an outside ophthalmologist for reduced vision and left eye pain for 10 days. Symptoms began following elective epithelial debridement and AM (dehydrated Eclipse) and bandage contact lens (BCL) placement in setting of recurrent erosions. There were no reported infiltrates or concern for infectious keratitis prior to epithelial debridement. The patient was using moxifloxacin 8 times daily, prednisolone 4 times daily, and artificial tears as needed. Vision was 20/20 in the right eye (OD) and 20/200, pinhole to 20/30 in the left eye (OS). The left eye had a corneal ulcer with a 1.2 × 2.5 mm epithelial defect with infiltrate and reduced corneal sensation (Fig. 1a). Cultures were collected from the infiltrate. She was initially treated with oral valacyclovir, erythromycin ointment, topical moxifloxacin, and discontinuation of prednisolone. Follow-up revealed a clinical worsening with diffuse injection, enlarged epithelial defect, and irregular infiltrate (Fig. 1b), leading to the initiation of hourly fortified amphotericin, tobramycin, and vancomycin.

Two weeks later, the patient had worsening ocular pain focused around the lacrimal gland which was inflamed. CT imaging to evaluate the extent of inflammation given clinical worsening revealed periorbital inflammation and intense enhancement along the lateral globe margin, concerning for preseptal cellulitis. Oral voriconazole was initiated,

* Corresponding author. 1 Medical Center Dr, Morgantown, WV, 26506, USA.
E-mail address: dedahshan@hsc.wvu.edu (L. Chen).

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leading to rapid improvement of pain. Cultures from the initial presentation finally identified *Fusarium* and amphotericin was switched to hourly natamycin. The ulcer continued to progress (Fig. 1c), prompting conjunctival flap, cryotherapy, and intracameral and intrastromal injection of voriconazole and amphotericin (Fig. 1d). The pain and inflammation rapidly improved following this surgery. The patient is pending conjunctival flap recession and penetrating keratoplasty.

2.2. Case 2

The second patient presented seven days following the presentation of the first case from the same practice. A 46-year-old male with a history of recurrent corneal erosion OS was referred for pain and blurry vision OS following elective epithelial debridement and AM with BCL placement three days prior. The patient did not have a history of trauma, infectious keratitis or eye surgeries prior to epithelial debridement. The patient was taking oral doxycycline, topical moxifloxacin, prednisolone acetate, and ketorolac OS. Vision was 20/20 OD and hand motion OS. Three peripheral corneal infiltrates with epithelial defects and a small hypopyon. Note it is difficult to see the hypopyon in Fig. 2. Treatment was initiated with hourly fortified topical amphotericin, tobramycin, and vancomycin. *Sistotrema biggsiae* was identified on the culture plate 26 days after collection. Follow-up at 1 month revealed improvement in vision to 20/30 OS and resolution of epithelial defect with remaining subepithelial scarring.

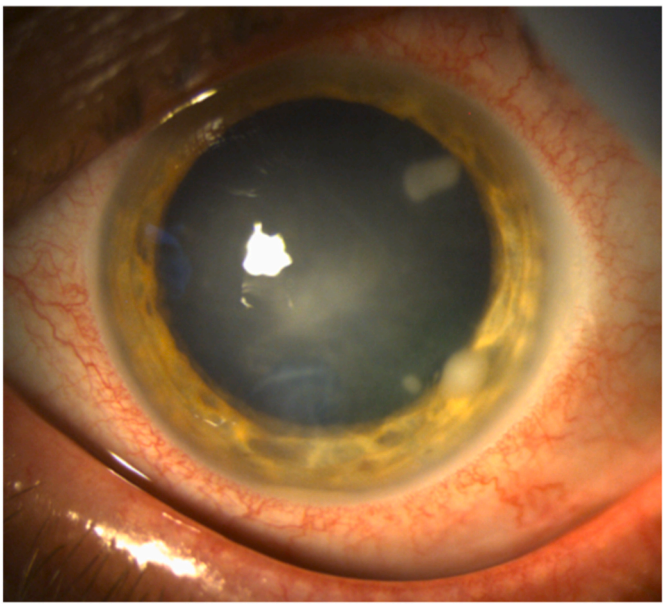

Fig. 2. *Sistotrema biggsiae seen on* slit lamp of the left eye in case 2. Examination on initial presentation showing a corneal ulcer with 3 infiltrates with epithelial defects, central haze, and hypopyon.

3. Discussion

AMT is increasingly and successfully used in treating patients for the reconstruction of ocular surfaces, persistent corneal epithelial defects, corneal ulcers, and bullous keratopathy.[1] Both patients had AMT with Eclipse, a dehydrated AM. Notably, this is air-dried and can be kept at room temperature, allowing for immediate use once activated with sterile saline, eliminating the need for a freezer with a 3-year shelf life. In contrast, cryopreserved AM is stored at −80° Celsius in media with ciprofloxacin, amphotericin B, and glycerol and can be in the form of nitrocellulose paper with a polycarbonate ring such as PROKERA (Biotissue).

Both cryopreserved and dehydrated AM have cases reported with associated microbial keratitis following implantation, including fungal keratitis with *Aspergillus*[2] and *Candida*.[3] There are more reported cases of bacterial keratitis following AMT than fungal keratitis.[2] However, from our literature review, there are no prior reported cases of *Sistotrema biggsiae* infection in people. *Sistotrema* genus is part of the *Hydnaceae* family, with most species of *Sistotrema* involving saprotrophs on decayed wood and ectomycorrhiza in symbiotic association with plant roots.[4] The Sistotrema cultures were plated in our clinic and sent to an external lab. The patient's presentation was consistent with fungal keratitis and no other microbe grew on initial cultures.

Fungal keratitis often presents with nonspecific features including conjunctival injection with or without epithelial defect but must be differentiated from other types of microbial keratitis. Fungal keratitis is associated with infiltrates with feathery margins, discoloration, and raised edges.[5] Cases are often complicated by delayed clinical diagnosis and laboratory confirmation leading to a protracted clinical course. Risk factors include contact lens wear, chronic surface disease, chronic broad-spectrum antibiotics, anesthetic abuse, immunosuppression, prior ocular surgery, and corneal trauma.

The interval duration of microbial keratitis following AMT reported in literature occurred within 28–347 days.[2] Management of fungal keratitis following AMT provides a unique dilemma, as AMT can be used in the treatment of refractory infectious corneal disease to promote wound healing and provide effective corneal reconstruction. Treatment of filamentous mycotic ulcers, namely Fusarium, has demonstrated better clinical outcomes with topical natamycin, compared to topical voriconazole.[6] Our patient with *Sistotrema* keratitis was effectively managed with hourly topical amphotericin, with complete resolution of the epithelial defect and good visual outcome. While it is not clear if *Sistotrema biggsiae* is specifically a filamentous fungal species, other Sistotrema species have been better described and recognized with hyphae.[4]

Following AMT, both patients used topical steroid and one was using topical ketorolac, which should be avoided due to the risk of corneal melting and perforation.[7] They were instructed to discontinue them upon presentation. Prompt discontinuation of corneal immunosuppression is critical to prevent a protracted clinical course with worsening microbial keratitis. The patient with *Fusarium* keratitis had ABMD, which is a contributing risk for recurrent corneal erosions and microbial keratitis. Neither patient had a history of diabetes or herpetic eye disease. We presume superficial keratectomy predisposed these patients to

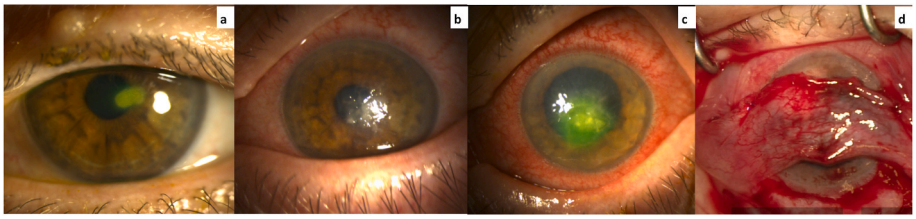

Fig. 1. *Fusarium* keratitis seen on slit lamp examinations of the left eye in case 1 (a–d). Fig. 1a shows the initial presentation of the corneal ulcer. Fig. 1b shows interval worsening at 2-week follow-up with irregular infiltrate and linear projections. Fig. 1c shows continued progression of the ulcer. Fig. 1d is following conjunctival flap and cryotherapy of case 1.

such rapid onset microbial keratitis. It is noted that both patients had AMT and BCL placed within one week prior to symptom onset. There is a possibility of BCL contributing to infection risk. There is limited literature regarding infectious keratitis in setting of BCL compared to sutures following AMT as infectious keratitis is not commonly reported in association with AMT. It is also noted that both patients presented from the same practice, however developed different fungal keratitis, with a possibility of inadequate instrument sterilization or AM contamination. We do not have knowledge of the manufacturing lab that produced the AM products for these patients to evaluate if this lab follows Good Tissue Banking practices. There were no reported patient risk factors regarding contact with wood or plant material to identify potential exposures for fungal keratitis in either case. Close follow up after AMT and BCL placement to monitor for infection development is essential.

4. Conclusions

To our knowledge, there are no prior reports of *Sisotrema biggsiae* infection. Both cases presented earlier than the interval duration of reported microbial keratitis following AMT, suggesting the importance of close follow-up for microbial keratitis after AMT. There is remarkable morbidity associated with fungal keratitis, with up to 25 % of affected eyes perforating or requiring surgical removal, with an estimated 60 % of patients becoming monocular despite treatment.[6] Moving forward, it is critical to ensure sterilization and utilization of cryopreserved AM products produced in accordance with Good Tissue Banking practices. Even though AMT can be effective in treating many corneal and conjunctival pathologies, the risk of keratitis following AMT should be considered, especially in patients with monocular vision.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Röck T, Bartz-Schmidt KU, Landenberger J, et al. Amniotic membrane transplantation in reconstructive and regenerative ophthalmology. *Ann Transplant*. 2018;23:160–165.
2. Fairaq R, AlBalawi E D, Al-Swailem S A. Microbial keratitis following self-retained cryopreserved amniotic membrane. *Case Rep Ophthalmol*. 2022:724–729.
3. Soda R, Fukuoka H, Sotozono C. A case of recurrent fungal keratitis post-amniotic membrane transplantation for corneal perforation. *Case Rep Ophthalmol*. 2022: 147–153.
4. Münzenberger B, Schneider B, Nilsson RH, et al. Morphology, anatomy, and molecular studies of the ectomycorrhiza formed axenically by the fungus *Sistotrema* sp. (Basidiomycota). *Mycol Prog*. 2012;11:817–826.
5. Hoffman JJ, Burton MJ, Leck A. Mycotic keratitis- A global threat from the filamentous fungi. *J Fungi*. 2021;7(4):273.
6. Prajna NV, Krishnan T, Mascarenhas J, et al. Mycotic Ulcer Treatment Trial Group. The mycotic ulcer treatment trial: a randomized trial comparing natamycin vs voriconazole. *JAMA Ophthalmol*. 2013;131(4):422–429.
7. Gokhale NS. Medical management approach to infectious keratitis. *Indian J Ophthalmol*. 2008 May-Jun;56(3):215–220.